128. The method according to Claim 10 wherein said disabling step includes substantially blocking the labeled repetitive nucleic acid fragments in the heterogeneous mixture by hybridization with unlabeled repetitive nucleic acid fragments that are substantially complementary to those in the heterogeneous mixture.

129. The method according to Claim 10 wherein said disabling step includes substantially blocking the repetitive nucleic acid sequences in the targeted chromosomal sequences by hybridization with unlabeled repetitive nucleic acid fragments complementary to those in the target.

130. The method according to Claim 10 wherein said disabling step includes either before or during the <u>in situ</u> hybridization step, substantially blocking the repetitive sequences in either the targeted chromosomal DNA, in the labeled nucleic acid fragments, or in both with unlabeled repetitive nucleic acid sequences, and/or by prereassociating the labeled nucleic acid fragments with themselves.

<u>REMARKS</u>

Applicants respectfully submit that the Specification has been amended to correct typographical and proofreading errors and to update the status of the priority applications.

Applicants respectfully submit that no new matter has been added by the amendments.

Claims 10-14, 16-17, 19, 22, 24-25, 36-42, 45-48, 51-53, 74-75, 102 and 103 were amended and dependent claims 127-130 were added to point out with more particularity what the claimed invention is. Applicants respectfully submit that the amendments do not add new matter to the application.

Applicants have amended Claim 12 to replace "homologous" with "complementary". Applicants respectfully point out that the phrase "substantially complementary" is used throughout the text, for example, at page 18, line 17, and that "substantially complementary" and "substantially homologous" are understood in the art to be essentially interchangeable terms as used in the context of the application.

Applicants have also amended all the independent claims remaining in the application, that is, Claims 10, 22, and 36 to indicate that the targeted sequences can be stained by the methods and compositions of this invention whether or not those sequences "are present at normal copy numbers for diploid or haploid cells or are at higher copy numbers". Applicants respectfully note that those amendments are supported throughout the Specification, for example, at page 23, lines 23-24.

Independent Claims 10 and 36 have further been amended to indicate that the labeled nucleic acid fragments of the chromosome-specific staining reagents are substantially

complementary to unique sequence regions in the targeted chromosomal DNA that have a complexity of at least 35 kilobases. In the instant Specification at pages 37-38, definitions for "complexity" and for "high complexity" are provided. "Complexity" is defined according to the standard for nucleic acid complexity as established by Britten et al. and further explained in Cantor and Schimmel [cites therefor are given at page 37, lines 14-16]. (Those two references were included in the Information Disclosure Statement submitted for this application.)

In Britten et al., the term "single-copy DNA" is also defined (at page 366) as "[t]he fraction of the DNA of a species which appears from its kinetics of reassociation to occur only once in a genome. The amount of single-copy DNA may depend upon the criterion used in the measurement." That definition of "single-copy" is basically the same as that for "unique" as used in the instant application. "Single-copy sequences" are specifically equated with "unique sequences" in the instant Specification at page 41, lines 9-11. Thus, Applicants respectfully submit that the term "complexity" and "single-copy" or "unique" in regard to nucleic acids have meanings understood in the art.

Further, Applicants respectfully submit that support for the amendments to Claims 10, 12, 16, 22, and 36 regarding the labeled nucleic acid fragments being substantially complementary

to targeted "unique sequences regions" can be found throughout the series of commonly owned applications on chromosome-specific painting from which the instant application claims priority. For example, in the first filed applications--U.S. Serial No. 819,314 (filed January 16, 1986, now abandoned) and U.S. Serial No. 937,793 (filed December 4, 1986, now abandoned), the specifications refer to the chromosome-specific staining reagents as collections of probes to "unique sequence regions" at page 12, lines 11-14 and page 13, lines 7-10, respectively.

Similarly, Applicants respectfully submit that the amendment phrase "complexity of at least 35 kb" is supported throughout the series of commonly owned applications on chromosome-specific painting. In those first filed applications (U.S. Serial No. 819,314 filed January 16, 1986, now abandoned; and U.S. Serial No. 937,793 filed December 4, 1986, now abandoned), the specifications state (in the sentence bridging pages 13-14 and at page 14, lines 18-21, respectively) that "[i]n one preferred embodiment where the heterogeneous mixture is generated on a fragment-by-fragment basis, the chromosomal DNA is initially cloned in long sequences, e.g., 35-45 kilobases in cosmids, or like vectors. After amplification the inserts are cut into smaller fragments and labelled for formation to a heterogeneous mixture." In the instant application on page 38, lines 9-11, it is noted that current hybridization techniques provide "a reliable, easily detectable signal with a probe of

about 40 kb to about 100 kb (e.g., the probe insert capacity of one or a few cosmids) targeted to a compact point in the genome." Applicants respectfully point out that "about 40 kb" is about the insert capacity of a cosmid.

In Claims 36-41, "[h]igh complexity" as a modifier of the claimed nucleic acid probes was deleted in view of the amendment in independent Claim 36 to the targeted unique sequences having "a total complexity of at least 35 kilobases (kb)". The term "high complexity" is defined in the Specification at page 37, lines 4-12, as meaning that a probe that is of "high complexity" contains "on the order of 50,000 (50 kb) or greater, up to many millions or several billions, of bases of nucleic acid sequences which are not repeated in the probe." (page 38, lines 4-7).

Applicants respectfully submit that amendments regarding the various alternative ways and timing of "disabling the hybridization capacity of repetitive sequences" as shown in new dependent Claims 127-130 are similarly well-supported in the series of commonly owned applications concerning chromosome-specific staining from which the instant application claims priority as well as in the instant application. For example, in the first filed applications, that is, in U.S. Serial No. 819,314 at pages 19-23 and U.S. Serial No. 937,793 at pages 20-24, there is a Section II entitled Disabling the Hybridization Capacity of Repetitive Sequences. Further, in Section II of those

applications (and Section VI in the latter) as well as other places in those Specifications, as for example respectively at page 10, lines 6-10 and at page 10, lines 9-18, wherein it is stated that the hybridization capacity of reptitive sequences "can be disabled in several ways, e.g., selective removal or screening of repetitive sequences from chromosome-specific DNA, selective blocking of repetitive sequences by prereassociation with complementary fragments, or the like" support the different types of steps useful in disabling the hybridization capacity of repetitive sequences. Further, the instant Application provides support for those claims and amendments in Section II at pages 60-72.

Support for the amendment to Claim 10 regarding "rendering visible the hybridized labeled nucleic acid fragments" is similarly supported throughout the chromosome-specific staining application. For example, support can be found for that amendment in the above-referenced first and second filed applications in Section III entitled Labeling the Nucleic Acid Fragments of the Heterogeneous Mixture at pages 24-25 and at pages 24-26, respectively, as well as in Section IV thereof entitled In Situ Hybridization at pages 26-31, particularly at page 27, lines 6 and 7 and at pages 27-32, particularly at page 28, lines 6 and 7. Parallel support can be found in the instant Specification in Section III at pages 72-74 and in Section IV at pages 74-80 as well as in many other places therein.

Thus, Applicants respectfully conclude that the amendments to the claims are well supported, and provide no new matter.

35 USC Section 112, First Paragraph Rejection of Claims 1-126

Claims 1-126 stand rejected under 35 USC Section 112, first paragraph. Applicants respectfully traverse that rejection.

Regarding the Examiner's statements concerning deposits of specific probes and libraries, Applicants respectfully point out that "biological materials need not be deposited when the invention can be practiced without undue experimentation from biological materials available in the prior art." Hybritech Inc. v. Abbott Laboratories, 4 USPQ2d 1001, 1011 (C.D. CA 1987), aff'd, 7 USPQ2d 1191 (Fed. Cir. 1988); see also, Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1025 (Fed. Cir. 1991) (in relation to genetically engineered cell lines; "If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required."); Feldman v. Aunstrup, 186 USPQ 108, 111 (CCPA 1975) cert. denied, 188 USPQ 720 (1976) (no deposits necessary when "the microorganisms used are known and readily available to the public."). Further, as the Federal Circuit has stated: "No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from

readily available starting materials through routine screening that does not require undue experimentation." [In re Wands, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988)].

Applicants further respectfully point out that 37 C.F.R. Section 1.802(b) states: "Biological material need not be deposited, inter alia, if it is known and readily available to the public or can be made or isolated without undue experimentation." Further, 37 C.F.R. Section 1.802(c) states: "The reference to a biological material in a specification disclosure or the actual deposit of such material by an applicant or patent owner does not create any presumption that such material is necessary to satisfy 35 U.S.C. 112 or that deposit in accordance with these regulations is or was required." Applicants respectfully submit that deposits of the probes pCV105 and PEM12 and/or of the genomic libraries for each of the human chromosomes are not necessary to provide an enabling disclosure for the claimed invention.

Applicants respectfully point out that the particular probes pCV105 and PEM12, in and of themselves, are not specifically claimed in this application nor are the genomic libraries for each of the human chromosomes. Applicants respectfully submit that the pCV105 and PEM12 probes are just representative of many different kinds of probes that could be used for detecting genetic rearrangements associated with chronic myelogenous leukemia (CML). Applicants respectfully point out

that many alternative types of probes could be also successfully used. For example, two other probes for the ABL and BCR genes, that is, other than pCV105 and PEM12 probes, respectively, could be used effectively, or alternatively staining at the same time with two BCR probes which flank the breakpoint region would indicate whether a rearrangement had occurred. In the former instance, one would look for co-localization of the BCR and ABL probes, and in the latter instance, the movement apart of the two probes. Further, Applicants respectfully submit that many other scenarios can be contemplated wherein "chromosome-specific painting" can be used to detect said genetic rearrangement, including, for example, probes which are in the vicinity of only one of the involved breakpoint regions or on both sides of both breakpoint regions; all such scenarios that employ chromosome-specific painting to detect said rearrangement, applicants respectfully submit, would be according to the claimed invention.

Other exemplary specific probes that could be used to detect CML-associated genetic rearrangements include those cited in the paper Arnoldus et al., Cytogenet. and Cell Genet., 54 (3-4): 108-111 (1990). That paper describes a cosmid clone Cos-abl-18 as containing a 40-kb (kilobase) fragment representing the 3' human ABL coding and 3' flanking sequences in the q34 band of chromosome 9; cited therein in relation to that clone is Heisterkamp et al., J. Molec. Appl. Genet., 2: 57-68 (1983). Also described therein is a cosmid clone for the BCR gene, Cos-

bcr-19-1 which contains a 34-kb fragment representing most of the first exon and the 5' half of the first intron of the BCR gene on chromosome region 22q11. Arnoldus et al. cites as a reference for that clone, Hermans et al., in Cancer Cells, Vol. 7, pp. 21-26 (Cold Spring Harbor Laboratory, Cold Spring Harbor 1989).

Therefore, in view of the fact that other comparable probes are available, Applicants respectfully submit that probes that can be used in chromosome-specific staining to detect genetic rearrangements diagnostic for CML are "known and readily available to the public", and therefore the representative probes pCV105 and PEM12 need not be deposited according to 37 C.F.R. section 1.802(b).

Further, Applicants respectfully submit that Applicants need not deposit such probes because comparable probes can be "derived from readily available starting materials through routine screening that does not require undue experimentation." [In re Wands, supra]. As indicated above, 37 C.F.R. Section 1.802(b) states in part: "[b]iological material need not be deposited, inter alia, if it . . . can be made or isolated without undue experimentation." Applicants respectfully submit that appropriate probes for detecting genetic rearrangements diagnostic for CML be isolated from "readily available starting materials" by conventional screening procedures.

Applicants respectfully note that the Examiner indicated that "a repeatable method" needs to be set forth in the

specification if the probes are not otherwise readily available to the public. Applicants respectfully point out that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Co. v. Brenner, 159 USPQ 335 (CADC 1968).] Applicants respectfully maintain that the methodology regarding screening to find appropriate probes that flank or extend partially or fully across known breakpoint regions is conventional and so well known that it need not be disclosed in an application. As the Federal Circuit (CAFC) stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ 2nd 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

Therefore, Applicants respectfully conclude on that point that the pCV105 and PEM12 probes need not be deposited because comparable probes and/or other probes that would function effectively to detect genetic rearrangements diagnostic for CML are either readily available or can be derived from readily available starting materials through routine screening procedures.

Similarly Applicants respectfully submit that the libraries listed on page 55 of the application as being deposited with the ATCC are representative of the type of libraries one could use and/or from which one could derive

particular probes useful for determining different kinds of genetic rearrangements. As indicated in the last line of page 54, "[a] representative list" of one type of chromosome-specific libraries is shown in Table I; those libraries were prepared from HindIII restriction enzyme fragments inserted into Charon 21A vectors. Applicants respectfully submit that it is standard methodology to prepare such libraries from flow-sorted chromosomes.

As indicated at pages 52-54 of the instant Specification, whole chromosomes can be isolated by direct flow sorting with or without the use of interspecific hybrid cell systems. "Chromosome sorting can be done by commercially available fluorescence-activated sorting machines, e.g., Becton Dickinson FACS-II, Coulter Epics V sorter, or special purpose sorters optimized for chromosome sorting or like instrument. . . . DNA is extracted from the isolated chromosomes by standard techniques. . . . Generation of insert libraries from the isolated chromosome-specific DNA is carried out using standard genetic engineering techniques. . . ." [page 52, lines 23-26 and page 53, lines 1-8].

As indicated in 37 C.F.R. section 1.802(c) (as quoted above) the actual deposit of biological materials "does not create any presumption that such material is necessary to satisfy 35 U.S.C. 112". Those deposits were made for the convenience of making them readly available to the research community as

recombinant DNA libraries constructed by the National Laboratory Gene Library Project as described in Van Dilla et al., Biotechnology, 4: 537 (1986).

Thus, Applicants respectfully conclude that although the Charon 21A vector libraries were deposited at the ATCC for convenient distribution to the research community, no presumption was thereby created that such deposits were necessary for enablement under 35 USC 112. As comparable libraries or probes (wherein probes in this context are considered labeled libraries) are readily available or can be derived from readily available starting materials through routine procedures, Applicants respectfully but vigorously maintain that deposits of the libraries listed on page 55 are not required for enablement according to 37 CFR 1.802(b).

Applicants respectfully question the Examiner's statements regarding the "procurement of targeted 'fetal' versus other chromosomal material as cited in Claim 4". As that claim has been cancelled from the instant application, Applicants respectfully submit that that point is obviated.

Applicants respectfully request the Examiner to reconsider the 35 USC section 112, first paragraph rejection of the Claims in view of the above amendments and remarks and to withdraw that rejection.

35 USC Section 112, First Paragraph Rejection of Claims 10-19, 21, 30, 31, 36-41, 44, 45, 50-53, 55, 56, 103, 108, 110, 115, 118 and 125

The remaining claims of those included in the heading immediately above, that is, Claims 10-19, 36-41, 45, 51-53 and 103 stand rejected under 35 USC section 112, first paragraph. Applicants respectfully traverse that rejection.

Applicants respectfully submit that the instant claims have been amended and now only refer to methods and compositions for detecting genetic rearrangements diagnostic for CML. Thus, Applicants respectfully submit that for the most part that said rejection has been obviated by the amendments to the claims.

Applicants respectfully submit that the instant invention in general provides a variety of approaches to detect genetic rearrangements by chromosome-specific painting whether known or unknown, and that the examples in the Specification of detecting CML are representative of detecting a known genetic rearrangement--the BCR-ABL fusion, the result of a translocation. As indicated above, many different probes could be used to detect that genetic rearrangement, which is the most defined type of genetic rearrangement as it has been mapped at the DNA level with great accuracy (as indicated below). Thus, as has been pointed out above, any of numerous probes can be used in the processes of the instant invention to detect genetic rearrangements diagnostic for CML. Applicants respectfully request the Examiner to reconsider the 35 USC 112, first paragraph rejection of the

above-identified claims in view of the above amendment and remarks.

35 USC Section 112, Second Paragraph Rejection of Claims 8-21, 27-31, 35-41, 43-45, 49-56, 98-101, 103, 106-119 and 125

The remaining claims of those included in the heading immediately above, that is, Claims 10-19, 36-41, 45, 51-53 and 103 stand rejected under 35 USC section 112, first paragraph. Applicants respectfully traverse that rejection.

In preface to the particular remarks regarding specific claims in the instant application, Applicants respectfully point out some case law on which they rely regarding indefiniteness of terms within claims. As the Federal Circuit stated in Andrew-Corp. v. Gabriel Electronics, Inc., 6 USPQ2d 201 at 2012-2013 (Fed. Cir. 1988):

> [T]erms in the claims such as "approach each other", "close to", "substantially equal", and "closely approximate", . . . are ubiquitous in patent claims. Such usages, when serving reasonably to describe the claimed subject matter to those of skill in the field of the invention, and to distinguish the claimed subject matter from the prior art, have been accepted in patent examination and upheld by the courts. As this court put it in Rosemount, Inc. v. Beckman Instruments Inc., 727 F.2d 1540, 1546-47, 221 USPQ 1, 7 (Fed. Cir. 1984):
>
> > Beckman attacks the claims as indefinite, primarily because "close proximity" is not specifically or precisely defined. . . . "to accept Beckman's contention would turn the construction of a patent into a

> mere semantic quibble that serves no useful purpose."

In Rosemount the district court found that "'close proximity' is as precise as the subject matter permits". Id In Seattle Box Co. v. Industrial Crating & Packaging, . . . 221 USPQ 568, 573-74 (Fed. Cir. 1984). . . . the court remarked that "substantially equal" is a term of degree, and that its acceptability depends on "whether one of ordinary skill in the art would understand what is claimed . . . in light of the specification", even if experimentation may be needed.

. . . See also Hybritech Inc. v. Monoclonal Antibodies, Inc., . . . 231 USPQ 81, 95 (Fed. Cir. 1986) ("the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more"), ...

The Manual of Patent Examining Procedure instructs examiners in a similar vein. See MPEP section 706.03(d):

> [An examiner] should allow claims which define the patentable novelty with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. [emphasis in original]

As Judge Learned Hand remarked in Musher Foundation, Inc. v. Alba Trading Co., Inc., 66 USPQ 183 at 186 (2d Cir. 1945):

> As in the case of any other claim, a product claim may, and indeed must, be read upon the specifications: its terms are no more than a shorthand from the fuller explanation which the specifications should contain.

Applicants respectfully submit that the terms used in the instant claims are "anchored in the specification" (Musher, id.), the text of which, including the representative examples and figures, as for example, Figure 11, provide "the fuller explanation" for the "shorthand" of the claims.

Applicants have amended Claim 12 to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants have amended Claim 12 to read that the nucleic acid fragments are "substantially complementary to unique sequence regions that flank and/or extend partially or fully across breakpoint regions known to be associated with genetic rearrangements identified with CML in chromosomal regions 9q34 and 22q11 of the human genome." Applicants respectfully submit that that language is "as precise as the subject matter permits." [Hybritech Inc. v. Monoclonal Antibodies, Inc. supra, at page 95.] Applicants respectfully submit that Claim 12 refers to breakpoint regions known to be associated with genetic rearrangements diagnostic for CML that are mapped at the DNA level in regions 9q34 and 22q11 of the human genome. Applicants, thus, respectfully submit that such "breakpoint regions" cannot be termed to be vague and indefinite in that they are specifically defined and mapped at the DNA level.

Further with regard to Claim 12, the Examiner questions the use of the term "homologous". Applicants respectfully point

out that the term "homologous" has been amended to read "substantially complementary". As indicated above, those terms are used interchangeably within the text of the Specification, and it was a proofreading error not to place "substantially" in front of homologous when the claim was originally written. Applicants respectfully point out that the term "complementary" has a standard meaning in the art.

Applicants respectfully submit that Claim 12 as amended indicates that the probes are designed to bind to nucleic acid sequences flanking or extending either partially or fully across the breakpoint regions. Those nucleic acid probes (since Claim 12 depends from claims dependent on Claims 10 and 11) have a complexity of at least 35 kilobases. Thus, Applicants respectfully submit that one of skill in the art would know based on the size of the probe used which is at least about 35 kilobases (kb), and the size of the breakpoint region, which as indicated (above and below) has been mapped, within what range the selected component probes need to be from the breakpoint region if it is designed to flank that region, or how far it can extend on either side of the breakpoint region, if it is designed to extend fully and/or partially across it, such that the staining pattern produced would be indicative of the genetic rearrangements, if present, for which the test has been created to identify. The Specification including representational

examples and the figures, for example, Figure 11, provide guidance on what types of patterns and distances work well.

Regarding Claim 10, Applicants have amended Claim 10 to indicate that said "one or more genetic rearrangements" are "diagnostic for CML". Applicants respectfully submit that the literature on human leukemia indicates that CML is "characterised by a consistent chromosomal abnormality, the Philadelphia (Ph) chromosome. The Ph chromosome results from a reciprocal translocation between chromosomes 9 and 22, designated t(9;22). . . " [Foon et al., in The Biology of Human Leukemia (Mauer, ed.) at page 73 (The John Hopkins University Press, 1990)]. As Tkachuk et al. state in Science, 250: 559 (26 October 1990): "Fusion of the proto-oncogene abl from the long arm of chromosome 9 with the bcr gene of chromosome 22 is a consistent finding in CML" citing de Klein et al., Nature, 300: 765 (1982); Groffen et al., Cell, 36: 93 (1984); and Heisterkamp et al. Nature, 306: 239 (1983); and then go on to indicate that the "genetic change leads to formation of a bcr-abl transcript that is translated to form a 210-kD protein present in virtually all cases of CML" [emphasis added] [Shtivelman et al., Blood, 69: 971 (1987); Konopka et al., Cell, 37: 1035 (1984); and Ben-Neriah et al., Science, 233: 212 (1986)]. Further, Tkachuk et al. indicate that "[i]n approximately 95% of cases the fusion gene results from a reciprocal translocation involving chromosomes 9 and 22, producing a cytogentically distinct small

acrocentric chromosome called Ph'" [emphasis added] [Nowell and Hungerford, Science, 132: 1497 (1960); Rowley, Nature, 243: 290 (1973); Grosveld et al., Mol. Cell Biol., 6: 607 (1986); Canaani et al., Lancet, 1: 593 (1984); Gale and Canaani, PNAS (USA), 81: 5648 (1984); and Konopka et al., ibid, 82: 1810 (1985)].

The definition of the term "diagnostic" in the American Heritage Dictionary: Second College Edition (Houghton Mifflin Company, Boston, 1991) is "serving to identify a particular disease; characteristic" or "of, pertaining to, or used in a diagnosis" wherein the medical term for diagnosis is "[t]he act or process of identifying or determining the nature of a disease through examination" or "[t]he opinion derived from such an examination". Applicants respectfully submit that the Philadelphia chromosome to be present in "approximately 95% of cases" of CML is a genetic rearrangement "serving to identify" that disease or be "characteristic" of CML and thus is "diagnostic for" CML.

Applicants further respectfully point out that as indicated in Figure 8, the breakpoint regions for CML for both chromosome 9 and 22 are specifically mapped. Applicants respectfully submit that such mapping as described in the first section of this response (under the heading 35 USC 112, First Paragraph Rejection of Claims 1-126) would allow anyone of ordinary skill in the art, who is informed concerning the chromosome-specific staining technology, to, by routine screening

procedures to find probes that would be sufficient to detect by chromosome-specific staining, genetic rearrangements that are diagnostic for CML. Applicants respectfully submit as indicated above that there are any variety of probes that can be used according to the methods of this invention to detect genetic rearrangements that are diagnostic for CML.

Applicants respectfully submit that the instant claims as amended do not refer to genetic rearrangements "associated with ALL".

Applicants thus, respectfully request that the Examiner consider this section 112, first paragraph rejection in light of the above amendments and remarks and withdraw that rejection.

35 USC Section 101 Rejection

Claims 51-53 stand rejected under 35 USC section 101. Applicants respectfully traverse this rejection.

Applicants respectfully submit that one with ordinary skill in the art would accept statements as to utility expressed in the instant application as valid and correct; thus, Applicants respectfully submit that the disclosed utility should be accepted as accurate unless some reason or authority in variance thereto can be advanced. [In re Gazave 154 USPQ 92 (CCPA 1967); In re Bundy, 109 USPQ 48 (CCPA 1981)].

The remarks that follow will indicate that it is established in the diagnostic community that differentiating

different diseases and/or disease states is important in determining the type of therapy that would be best suited for a patient. For example, the presence of the Ph^1 chromosome in CML is of prognostic importance, for it indicates a better response to chemotherapy and a significantly longer survival than for Ph^1-negative patients. [Bartram et al., Nature, 306: 277-280 (17 Nov. 1983)].

Another example is indicated in the instant Specification at page 122, lines 14-16: "The acquisition of an additional Ph^1 is the most frequent cytogenetic event accompanying blast transformation, and its cytogenetic detection may herald disease acceleration." As indicated at page 122, lines 13-14 that event, detected in the experiments therein described by chromosome-specific staining, was not detected by standard cytogenetics. As indicated in Mauer, A.M., "Clinical Features of Human Leukemia," in The Biology of Human Leukemia (Mauer, A.M. ed.), The John Hopkins University press (1990) at page 13:

> The treatment of CML in chronic phase has generally been approached with palliative intent. . . . Single-drug treatment with the alkylating agent busulfan or the antimetabolite hydroxyurea is the standard approach. . . . Treatment during the blast crisis is determined by the blast cell phenotype and will be according to protocols for ALL or AML. . . .

[Citations omitted.] Thus, determination of when the blast crisis is about to occur, Applicants respectfully submit, would

be very important for figuring out when to change the type of therapy required.

Once CML is diagnosed, the disease is typically initially well-controlled by palliative chemotherapy and/or biologic therapy such as interferon [Advances in Understanding Genetic Changes in Cancer; Impact on Diagnosis and Treatment Decisions in the 1990s, Institute of Medicine (Rowley et al.; National Academy Press; Wash. D.C. 1992); hereinafter cited as "Advances"]. If the patient is a suitable candidate, appropriate age, and an available donor exists, bone marrow transplanation is the treatment of choice. The optimal timing of transplant, a procedure with 20-30% mortality, is currently not settled. Patients may persist in chronic phase for years with a good quality of life, only unpredictably to enter blast crisis, a phase of the disease with very poor outcome even with transplanation. Thus chromosome-specific painting to detect when blast crisis is likely to occur provides an opportunity for therapeutic intervention to be optimized. [Advances.]

Further, Applicants respectfully submit that as evidenced by the accompanying affidavit from Daniel Pinkel, chromosome-specific painting is very important in being able to test cells from a patient on a cell by cell basis whereas prior art cytogenetic analysis did not allow such testing. As indicated in the accompanying affidavit, prior art methods as traditional karyotyping and Southern blots are not nearly as

sensitive as chromosome-specific painting for detecting abnormal cells in a patient.

The detection of minimal residual disease is very important. For example, following a bone marrow transplantation in a CML patient, a substantial fraction of patients relapse, often several years following the procedure. It is estimated that at the time of a bone marrow transplant, most patients in chronic phase CML have a tumor burden of about 10^{12} cells. [Advances.] Tradiational cytogenetics can be used to detect persistence of the Ph^1 at a frequency wherein a patient even if they are in cytogenetic remission could still have huge tumor burden of as much as maybe 10^9 cells. [Advances.] More sensitive tests to detect relapse at an earlier stage would identify patients who need additional therapy. [Advances.] Thus, the more sensitive testing provided by chromosome-specific painting to detect residual disease would be an important aid for determining therapy.

Further, chromosome-specific painting can be used to determine whether or not a certain therapy like alpha interferon is helpful or not for a certain patient, in that the success of individual therapy can be determined by being able to detect the number of abnormal cells remaining after therapy. Applicants respectfully submit the such an example is representative of the type of therapy decisions one monitoring a patient with a disease, such as CML, would have to make and for which the

information provided by chromosome-specific painting would be very helpful.

Applicants therefore conclude on this point, respectfully, that one of ordinary skill in the art would be aware of the utility that chromosome-specific painting to detect genetic rearrangements diagnostic for CML, as claimed in this application, would provide to the medical and research community. Applicants respectfully request the Examiner to reconsider the 101 rejection in view of the above amendments and remarks and to withdraw that rejection.

35 USC Section 102(b) Rejection over Langer-Safer et al.

Remaining Claims 22, 24-26, 42, 46, 47 and 74-75 stand rejected under 35 USC 102(b) as being anticipated by Langer-Safer et al. Applicants respectfully traverse this rejection.

Applicants respectfully submit that the amendments to the claims more particularly point out the subject matter of the instant invention and obviate the objections that the Examiner had as to the terms "vicinity" and "suspected" genetic rearrangements. Applicants respectfully submit that the Langer-Safer et al. article concerns the mapping of low complexity probes to Drosphila melanogaster polytene chromosomes. In polytene chromosomes the unusual situation occurs wherein the target size is repeated about 1000 times, and thus, there are many copies of the target to which a probe can hybridize.

Applicants respectfully submit that Langer-Safer et al. concerns individual hybridizations of probes from single clones and is thus representative of prior art single clone hybridizations.

Further, Langer-Safer et al. is inapposite to the instant invention in that the methods of Langer-Safer et al. are not able to stain targeted sequences present at normal copy numbers for diploid or haploid cells. The targeted sequences in Langer-Safer et al. are amplified about 1000 times over that normally found in haploid or diploid cells. All the independent claims now pending in the instant application have been amended, as noted above, to indicate that the methods and compositions of this invention stain targeted sequences "whether the targeted sequences are present at normal copy numbers for diploid or haploid cells or at higher copy numbers." The targeted sequences of Langer-Safer et al. are those of polytene chromosomes which, as evidenced below, are not diploid or haploid.

Enclosed is a copy of the pertinent pages from Lewin (ed.), Genes, (2d Edition John Wiley & Sons, Inc. 1985). That reference indicates at pages 464-465 that polytene chromosomes are outside the definition of haploid and diploid. At the bottom of column one, page 464, the structure of polytene chromosomes is described wherein "[e]ach is produced by successive replications of a synapsed diploid pair. The replicas do not separate, but remain attached to each other in their extended state." Applicants thus respectfully submit that the polytene chromosomes

as targeted in Langer-Safer et al. do not have sequence copy numbers that are normal for haploid or diploid cells.

Thus, Applicants respectfully request the Examiner to reconsider the 35 USC Section 102(b) rejection over Langer-Safer et al. in view of the above amendments and remarks and to withdraw that rejection.

35 USC Section 102(b) Rejection over Montgomery et al.

Remaining Claims 22, 42, 46, 47, 74 and 102 stand rejected under 35 USC Section 102(b) as being anticipated by Montgomery et al. Applicants respectfully traverse that rejection.

Applicants respectfully submit that the claims have been amended to more particularly point out and distinctly claim what Applicants regard as their invention, and that all the independent claims have been amended to indicate that the methods and compositions of this instant invention can stain targeted chromosomal material whether the targeted sequences are present at normal copy numbers for diploid or haploid cells or at higher copy numbers.

The Montgomery et al. article concerns mapping the position of a nucleic acid sequence that is highly repeated (perhaps hundreds or thousands of times above normal levels) in cancer cells. Their procedure was not able to detect less highly amplified sequences in Southern blots, and certainly not a target

sequence at a normal level of genomic abundance by in situ hybridization.

Montgomery et al. specifically teaches away from the instant invention in the sentence bridging pages 5727-5728 where it is stated: "Our failure to observe amplified sequences in the SH-SY5Y line . . ., even though it may contain a single, small ABR, is most easily explained by its degree of amplification being too low to be detected by the methods used here." That statement refers to an inability to detect said ABR known to be a site of "low level DHFR gene amplification in antifolate-resistant Chinese hamster lung cells" [page 5727, column 2, lines 24-25] in said neuroblastoma cell line [SH-SY57 line] in Southern blots rather than by in situ hybridizations. It can be presumed, Applicants respectfully submit, that the paper presents the most sensitive results that Montgomery et al. could achieve in view of the absence of any report of successful in situ hybridization. Thus, the failure to detect said low level amplified sequences by Southern blot, Applicants respectfully submit, teaches away from using the approach therein to detect targets at normal levels in Southern blots and, even more strongly, teaches away from using that approach for in situ hybridizations. Therefore, Montgomery et al., Applicants respectfully submit, teaches that its methodology cannot be used to stain less amplified sequences than the highly amplified sequences of the HSRs and DMs that were

stained according to the paper, and certainly not normal, nonamplified nucleic acid sequences by in situ hybridization.

What suggestion is there in Montgomery et al., Applicants respectfully question, for staining sequences at normal levels of genomic abundance for haploid or diploid cells? Montgomery et al. is concerned with aberrant conditions of cancer cells wherein the sequences are amplified sufficiently that, for example, chromosome 7 under traditional karyotyping by Giemsa staining is greatly enlarged [Fig. 3(a)], banding regions are abnormal and/or double minute chromosomes are present. Montgomery et al., Applicants respectfully submit, represesent an isolated setting wherein sequences that are amplified are the concern, that is, at genomically abnormal levels for haploid or diploid cells. Further, as indicated above, Montgomery et al. could not detect in Southern blots, for whatever the reason, "amplified sequences in the SH-SY5Y line . . . even though it may contain a single, small ABR" [abnormally banding region] citing as an explanation that "its degree of amplification" is probably too low for detection "by the methods used here." [Emphasis added.] Applicants respectfully submit that Montgomery et al. in no way provides guidance as to what aspect of the methods used might be changed in order to detect said amplified sequences of the ABR by Southern blots, let alone nonamplified sequences at a genomically normal level by in situ hybridization.

Whatever Montgomery et al.'s results, they were unrecognized and unappreciated in regard to the concept of chromosome-specific painting of whole chromosomes, subsets of chromosomes and/or regions of specific chromosomes as taught by the instant invention. "[A]nother's experiment, imperfect and never perfected, will not serve either as anticipation or as part of the prior art, for it has not served to enrich it." Fromson v. Advance Offset Plate, Inc., 225 USPQ 26 at 33 (Fed. Cir. 1985) (quoting Picard v. United States Aircraft Corp., 53 USPQ 563, 566 (2d. Cir. 1942), cert denied, 311 US 651 (1942).]

An invention may be be patentable even if it embodies a solution to a problem where the solution seems simple and obvious with the benefit of hindsight. National Sponge v. Rubber Corp., 128 USPQ 320 at 324 (9th Cir. 1961), cert. denied, 32 USPQ 703 (U.S. 1962); Saf-Gard Products v. Service Parts, 190 USPQ 455 (9th Cir. 1976). It is a well tread principle of patent law that the use of hindsight in interpreting a reference is improper. The information conveyed by prior art is crystallized as of the date it is made public. That information cannot be corrected or altered to convey information or facts later acquired by others skilled in the art. Pfizer v. International Rectifier, 207 USPQ 397 (D.C.C. Cal. 1980), aff'd, 217 USPQ 39 (9th Cir. 1982).

> It is difficult but necessary that the decision maker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who

> is presented only with the references, and who is normally guided by the then-accepted wisdom in the art. W.L. Gore v. Garlock, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983). It is impermissible to first ascertain factually what appellants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants invention from such prior art. In re Shuman, 361 F.2d 1008, 1012, 150 U.S.P.Q. 54, 57 (C.C.P.A. 1966).

Gore and Shuman are cited with approval in Panduit Corp. v. Dennison Manufacturing Co., 744 F.2d 1082, 227 U.S.P.Q. 337 (Fed. Cir. 1986).

Thus, Applicants respectfully conclude that as Montgomery et al. was employing the most sensitive detection system known at the time and could not even detect by Southern blotting some amplified sequences (ABR sequences) using those methods, and further was only concerned with detecting highly amplified sequences. Montgomery et al. provided no motivation to detect sequences at normal levels for haploid or diploid cells. Applicants respectfully conclude that Montgomery et al. teaches away from the instant invention.

Provisional Rejection under the Judicially Created Doctrine of Obviousness-Type Double Patenting

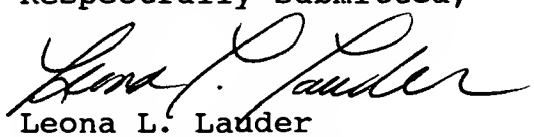
The pending claims stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the claims of co-pending application Serial No. 07/497,098. Applicants respectfully recognize the obligation

under 37 CFR 1.78(b) to eliminate conflicing claims when filed in two or more applications. Applicants respectfully submit that once patentable subject matter is determined to be allowable that they intend to cancel all conflicting claims in the commonly owned, co-pending applications.

CONCLUSION

Applicants respectfully request the Examiner to reconsider the rejections of the instant claims in view of the above remarks, and to withdraw the same. Applicants respectfully submit that the pending claims are in condition for allowance and earnestly solict that they be promptly allowed.

Respectfully submitted,



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Dated: